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(54) Title: MAGNESIUM OMEPRAZOLE

(57) Abstract: Improved process to produce magnesium omeprazole substantially amorphous with pharmaceutically acceptable low level of methanol and solid pharmaceutical compositions.

MAGNESIUM OMEPRAZOLE**5 FIELD OF THE INVENTION**

The present invention relates to an improved form of magnesium omeprazole, a process for making same, and pharmaceutical compositions same.

10

BACKGROUND OF THE INVENTION

15 The compound known under the generic name omeprazole is described in European patent 0005129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity in mammals and man. Omeprazole may be used
20 for prevention and treatment of gastric acid related disorders and gastrointestinal inflammatory diseases in mammals and man, including for example gastritis, gastric ulcer and duodenal ulcer.

25

The term "omeprazole" as used in this specification designates the neutral form of the compound, that is the form without a salt-forming cation present.

30

Certain salts of omeprazole are described in European patent 0124495.

5

In EP 0124495, example 5 specifically discloses the synthesis of magnesium omeprazole dihydrate, and example 6 specifically discloses the synthesis of magnesium omeprazole anhydrate. Manufacturing of the described
10 magnesium omeprazole salts presents significant difficulties.

15

The process of manufacture and isolation of the dihydrate according to example 5 is relatively complex. It requires making the sodium salt, adding a solution of magnesium chloride to obtain a precipitate, removing water by centrifuging the precipitate, washing the precipitate with deionized water until no Cl⁻ is detectable, drying in air, grinding, and the drying in vacuum at 40°C
20 for 24h. Moreover, because the resulting magnesium omeprazole dihydrate is crystalline, the rate of dissolution in intestinal fluid is relatively slow, unless the material is milled to a relatively fine particle size.

25

The process of making the anhydrate according to example 6 is simpler.

30

Magnesium is reacted with methanol to give a solution of magnesium methoxide in methanol. The solution is added to a solution of omeprazole in methanol, the quantity of omeprazole being one mole for each two moles of
30 magnesium. The methanol is then evaporated to give a crystalline solid,

which is magnesium omeprazole anhydrate. However, the anhydrate as made
5 by this process is also not without a problem. As the magnesium omeprazole
precipitates from the solution upon evaporation of the methanol, residual
methanol is entrapped in the solid particles and cannot easily be removed by
evaporation. Methanol is toxic and high levels are generally considered
10 unacceptable in pharmaceutical chemicals.

Canadian patent 2166794 describes what is said to be an improved form of
15 magnesium omeprazole dihydrate, which has a higher degree of crystallinity
than that of example 5 of EP 0124495. This form has a methanol content of
less than 0.1%. However, like the product of example 6 of EP 0124495, it is a
crystalline dihydrate, and the process of manufacture is relatively complex.

20

According to Canadian patent 2166794, the degree of crystallinity of a sample
made according to example 6 of EP 0124495 was 67%, whereas the degree
of crystallinity of the improved form is at least 70%.

25

Canadian patent application No. 2254572 discloses improved processes for
the production of magnesium omeprazole crystalline dihydrate. The
disclosure reviews the prior art, and in particular, in relation to the anhydrate of
30 example 6 of EP 0124495, states as follows: "This procedure cannot be

practised on a large scale because of the need to evaporate to dryness. It has
5 been found that unacceptable and potentially dangerous amounts of methanol
become trapped in this solid, making it pharmaceutically unacceptable." The
processes of Canadian patent 2254572 are again relatively complex.

10 Improved processes for the production of magnesium omeprazole crystalline
dihydrate are also described in PCT Publication No. WO 97/4114. The degree
of crystallinity of the product of example 1 is said to be 80%. Again, the
15 processes disclosed are relatively complex.

In summary, the only magnesium omeprazole according to the prior art that
has an acceptably low level of methanol is magnesium omeprazole crystalline
20 dihydrate, which has a degree of crystallinity of 67% or higher and is produced
only by relatively complex processes.

In light of the foregoing, the object of the present invention is to produce
25 magnesium omeprazole that has acceptably low levels of methanol, but is
substantially amorphous (non-crystalline), and can be produced by a simple
process.

30

BRIEF SUMMARY OF THE INVENTION

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Magnesium omeprazole of the present invention is made by reacting magnesium in a lower alcohol to form magnesium alkoxide, adding omeprazole in a quantity of about two moles per mole of magnesium, and
10 flash-evaporating the alcohol, so as to form a solid precipitate without allowing the growth of crystals or particles that entrap the alcohol at unacceptable levels. The resulting material is substantially amorphous (non-crystalline).

15

DETAILED DESCRIPTION OF THE INVENTION

In the process of manufacture of magnesium omeprazole according to the
20 present invention, magnesium is reacted in a lower alcohol, preferably methanol, to form a solution of magnesium alkoxide in the alcohol.

The atomic weight of magnesium is 24.3 and the molecular weight of
25 omeprazole is 345.4. Since magnesium is divalent, the amount of magnesium required to convert 345.4 grams of omeprazole to magnesium omeprazole is 12.15 grams.

30

Hence 35.2 grams of magnesium is needed to convert 1 kilo of omeprazole to
5 magnesium omeprazole.

The process of converting 1 kilo of omeprazole to magnesium omeprazole
thus begin with reacting 35.2 grams of magnesium in a lower alcohol,
10 preferably methanol. The minimum amount of methanol needed to fully react
and dissolve 35.2 grams of magnesium is about 1000 grams.

15 When the magnesium is immersed in the alcohol, the reaction will be evident
from the generation of hydrogen bubbles, and the reaction will be complete
when all the magnesium has been consumed and the effervescence has
ceased. All of the magnesium will then be present as magnesium alkoxide in
20 the alcohol (i.e. magnesium methoxide in methanol, if methanol is used as the
alcohol).

The omeprazole can then added directly to the magnesium alkoxide solution.
25 Alternatively, the omeprazole may first be dissolved in an alcohol or another
organic solvent that is miscible with the alcohol used to make the magnesium
alkoxide, and the resultant solution may then be added to the magnesium
alkoxide solution.

30

Where methanol is used as the sole solvent, a total of only about 1.5 kilos is
5 needed for converting 1 kilo of omeprazole to magnesium omeprazole in
solution by the methanol.

Hence, using quantities based on 1 kilo of omeprazole, the simplest and best
10 procedure is to react 35.2 grams of magnesium in about 1.5 kilos of methanol,
wait until the magnesium has been fully reacted, and then add the 1 kilo of
omeprazole to the solution and stir to dissolve. The resulting solution will be a
15 solution of magnesium omeprazole equivalent to 1 kilo of omeprazole in
methanol.

In order to obtain solid magnesium omeprazole that is substantially free of
20 organic solvent (i.e. substantially free of methanol, if methanol is used), it is
then necessary to eliminate the solvent.

It has been found that this can be done by "flash-evaporating" the solvent.
25 Flash-evaporating will be understood to mean evaporating in such a way as to
avoid the precipitation of crystals or large particles which entrap the alcohol.

One method of flash-evaporating the solvent is to mix the solution into a solid
5 excipient such as, for example, microcrystalline cellulose so that a damp mass
is formed. The mass can then be dried in a conventional oven, a fluid bed
drier, or under vacuum to remove the solvent. Because the solution has been
dispersed throughout the solid excipient, as the solvent evaporates, the
10 omeprazole magnesium is deposited as a thin layer over the surface of the
particles of the solid excipient and does not precipitate as crystals or large
granules, so that there is little or no entrapment of solvent.

15 The preferred way of flash-evaporating the solvent is by spray-drying the
solution.

20 It has been found that, by such process, magnesium omeprazole can be made
having a residual solvent content substantially lower than can be achieved by
simply evaporating the solvent from the solution under vacuum.

25 The residual organic solvent content by weight of the magnesium omeprazole
made according to the present invention will be under 7%, preferably under
5%, more preferably under 2%, and most preferably under 1%.

30

The degree of crystallinity of the obtained product can be measured with
5 powder X-ray diffraction (XRD) as described in WO97/4114 as follows: A thin
layer of the triturated sample is smeared onto a cut silicon single crystal zero
background holder which is rotated during the measurement. Cu K α radiation
and constant or automatic antiscatter and divergence slits are used to obtain a
10 diffractogram with 2θ from 1 or 2° to at least 35°.

The degree of crystallinity is calculated with the formula
15 degree of crystallinity = $100 + C/(A+C)$

C= the area from the peaks in the diffractogram ("the crystalline area"),

A= the area between the peaks and the background ("the amorphous area").

20

Area calculations are performed for 2θ between 4-33°. The lowest intensity
value found in this interval is chosen as the constant background and
subtracted from the area A. When constant slits are used, the increased
25 background at low angles due to the influence from the primary beam is also
subtracted from the area A.

30

5 The degree of crystallinity of magnesium omeprazole according to the present invention is under 67%, as compared to 67% or higher for magnesium omeprazole crystalline dihydrate according to the prior art.

10 The degree of crystallinity will preferably be under 60%, more preferably under 50%, and most preferably under 25%.

15 If the magnesium omeprazole of the present invention is made in an environment and using excipients (including the air or other gas used for drying in the spray-dry process) that is completely free of water, the magnesium omeprazole will be anhydrous. However, pure anhydrous magnesium omeprazole is hygroscopic and it will readily absorb water from air
20 until it reaches an equilibrium water content of about 5% to 8%, depending on the relative humidity of the air. This is not problematic, as it does not adversely affect stability.

25 The magnesium omeprazole of the present invention will be further processed into pharmaceutical compositions such as, for example, tablets for oral administration. The tablets will preferably be enteric coated to protect the magnesium omeprazole from the effects of gastric acid.

30

The invention will be further understood from the following examples, which
5 are intended to be illustrative and not limiting of the invention.

EXAMPLE 1

10 1.76 g of pure magnesium was added to 800 g of methanol in a 1000 mL
glass flask. The flask was closed with a loose-fitting stopper (loose to allow
hydrogen gas to escape), and the flask was allowed to sit overnight.

15 The next morning it was observed that the magnesium had all been consumed
and that the effervescence had ceased, resulting in a slightly hazy solution of
magnesium methoxide in methanol. 50 grams of omeprazole was then added
20 to the contents of the flask and the contents were stirred for several minutes
until the omeprazole dissolved to form a solution of magnesium omeprazole in
methanol.

25 EXAMPLE 2

To produce a reference sample of magnesium omeprazole anhydrate
according to the prior art (i.e. example 6 of EP 0124495), about 20% of the
30 solution from step 2 was transferred to a 1000 mL beaker. The beaker was

then placed in a vacuum oven for drying under vacuum at 50°C for a period of
5 4 hours. At the end of this time, a solid material remained that had no evident
odour of residual methanol. This solid material was tested to determine the
level of residual methanol, which was found to be 7.2% by weight.

10 EXAMPLE 3

To produce magnesium omeprazole of the present invention, the balance of
15 the solution of Example 1 was spray-dried on a Yamato® spray-dryer, using
an inlet air temperature of about 140°C and outlet air temperature of about
70°C.

20 The resulting dry material was a fine powder, which appeared non-crystalline
and also had no evident odour of residual methanol. The powder was tested
to determine the level of residual methanol, which was found to be 0.7%.

25 This powder was examined for crystallinity by powder X-ray diffraction, and it
was found that the powder was substantially amorphous (non-crystalline),
having a degree of crystallinity of under 25%.

30

EXAMPLE 4

5

The following ingredients were mixed together in the proportions shown:

10	Magnesium omeprazole	21.
	Anhydrous lactose	131.
	Croscarmellose sodium	6.4
	Magnesium stearate	<u>1.6</u>
15		160.

The mixture was compressed into tablets having a weight of 160 mg per tablet, so that each tablet contained 21 mg of magnesium omeprazole, which is equivalent to about 20 mg of omeprazole.

A sub-coating comprising hydroxypropyl methylcellulose dissolved in water was then applied to the tablets by spray-application in a side-vented coating pan.

An enteric coating was then applied over the sub-coating by spray-application of methacrylic acid copolymer aqueous dispersion, with triethyl citrate dissolved therein as plasticizer.

WHAT IS CLAIMED IS:

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1. A process of producing magnesium omeprazole, said process comprising the steps of:

10

- i) reacting magnesium with a lower alcohol to produce magnesium alkoxide in solution in the lower alcohol as solvent,
- ii) adding omeprazole to the solution, the amount of omeprazole being about 2 moles per mole of magnesium, and
- 15 iii) flash-evaporating the solvent.

20

2. A process of claim 1 wherein the lower alcohol is methanol.

3. A process of claim 1 wherein the flash-evaporation is done by spray-drying the solution.

25

4. Magnesium omeprazole that is substantially amorphous having a residual organic solvent content of less than 7% by weight.

30

5. Magnesium omeprazole having a degree of crystallinity of under 67% and a residual organic solvent content of less than 7% by weight.

- 5 6. Magnesium omeprazole of claim 4 or 5 having a residual organic solvent content of less than 5% by weight.
- 10 7. Magnesium omeprazole of claim 4 or 5 having a residual organic solvent content of less than 2% by weight.
- 15 8. Magnesium omeprazole of claim 4 or 5 having a residual organic solvent content of less than 1% by weight.
- 20 9. Magnesium omeprazole of any of claims 4 to 8 having a degree of crystallinity of under 60%.
- 25 10. Magnesium omeprazole of any of claims 4 to 8 having a degree of crystallinity of under 50%.
11. Magnesium omeprazole of any of claims 4 to 8 having a degree of crystallinity of under 25%.
- 30 12. A solid pharmaceutical composition for oral administration comprising magnesium omeprazole of any of claims 4 to 11.

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13. A composition of claim 12 in the form of a tablet.

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14. A composition of claim 13 wherein the tablet is enteric coated.

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INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,A	WO 00 30612 A (ASTRAZENECA) 2 June 2000 (2000-06-02) the whole document	1,4

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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